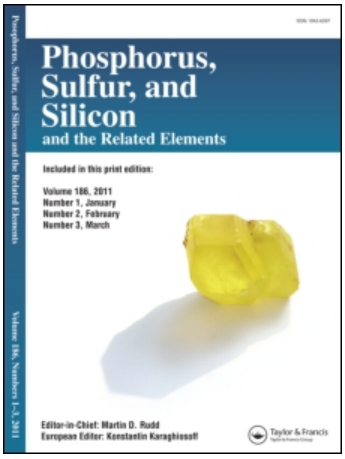

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Diastereo and Enantioselective Synthesis of 1,2-Diols Promoted by Electrophilic Selenium Reagents

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*Here we report the first example in which the phenylseleno group is directly substituted by a hydroxy function. The reaction is promoted by the $PhSeOSO_3H$ generated "in situ" by oxidation of $(PhSe)_2$ with $(NH_4)_2S_2O_8$ at reflux in a 3:1 mixture of MeCN-H_2O. Interestingly the reaction can be performed in "one pot" using a catalytic amount of diselenide affording the corresponding diols (**5** and **6**) with good yield and good level of diastereo- and enantioselectivity.*

Keywords Asymmetric synthesis; catalysis; selenium; 1,2-Diols

INTRODUCTION

In recent years, we,[1] as well other research groups[2] have studied the application of electrophilic selenium species in diastereo and enantioselective synthesis using chiral non racemic selenenylating species extensively. One of the most attractive features of the selenium chemistry is the possibility to manipulate the organoselenium moiety affording, depending on the structure of the molecule, elimination,[3,4] or substitution derivatives.[5]

A different approach for the synthesis of enantiomerically pure β-hydroxyselenides is now proposed starting from unsatured natural terpenes. According to the "chiral pool approach," terpenes can be considered convenient starting materials in asymmetric synthesis because they are commercially available, not expensive and generally easily accessible in both the enantiomeric forms.

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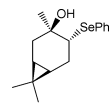
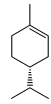
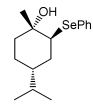
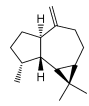
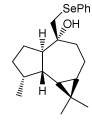
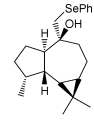
Address correspondence to C. Santi, Dipartimento di Chimica e Tecnologia del Farmaco. Sezione di Chimica Organica, University of Perugia, via del Liceo, 06100 Perugia, Italy. E-mail: santi@unipg.it

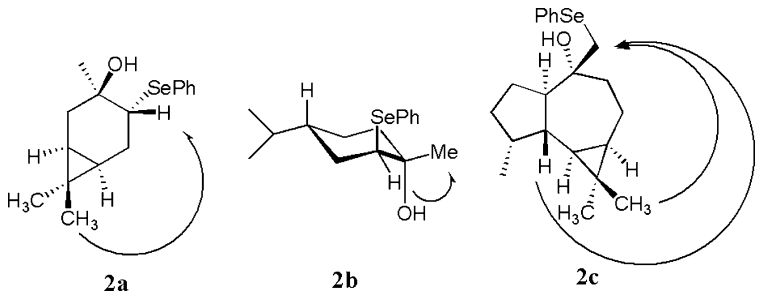
TABLE I Reaction of Terpenes with PhSeOTf and H_2O at 20°C

Entry	Terpene	Products	Time (h)	Yield
1	 **1a**	 **2a**	24	50% **2a**
2	 **1b**	 **2b**	24	70% **2b**
3	 **1c**	 **2c**  **3c**	40	40% 2c 56% **3c**

RESULTS AND DISCUSSION

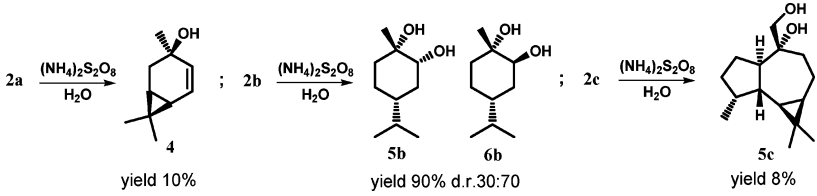
The hydroxyselenenylation of unsatured terpenes can be obtained by treatment with PhSeOTf in a 3:1 mixture of MeCN-H_2O at 20°C. In a typical experiment, silver triflate (1.1 mmol) was added to a solution of PhSeBr (1.0 mmol) in MeCN (2.0 mL) at 0°C. The reaction was stirred for 30 min and then 1.0 mmol of the terpene **1a–c** was added in a 1:1 mixture of MeCN-H_2O (2.0 mL). The mixture was allowed to gradually reach room temperature. The progress of the reaction was monitored by TLC and GC-MS. Reaction times, chemical yields and diastereomeric ratios are reported in Table I.

Starting from (+)-3-carene **1a** (Table I, entry 1) and (+)-*p*-menth-1-ene **1b** (Table I, entry 2) the reaction leads to the stereospecific formation of compounds **2a** and **2b**, respectively, deriving from the attack of the electrophilic selenium reagent from the less hindered face of the double bond. When the addition occurs in an exocyclic olefin, as in the case of (+)-aromadendrene **1c** (Table I, entry 3), a lower diastereoselectivity has been observed and the two isomers **2c** and **3c** were obtained in a ratio of 42:58. The absolute configurations reported in Table I were assigned by proton NMR on the basis of the coupling constants and some n.O.e. correlations that are summarized in Scheme 1.



SCHEME 1

We already observed that alkyl phenyl selenides, by reaction with ammonium persulfate, suffer deselenenylation giving the substitution[3] or elimination[5] products depending on the reaction conditions and the nature of the substrate. Treatment of **2a–c** and **3c** with ammonium persulfate in a 3:1 mixture of MeCN-H_2O at 85°C affords the formation of the corresponding 1,2-diols in good yields only in the case of the menthene derivative **2b**. In all the other cases, only small amounts of the deselenenylation products were observed (Scheme 2).

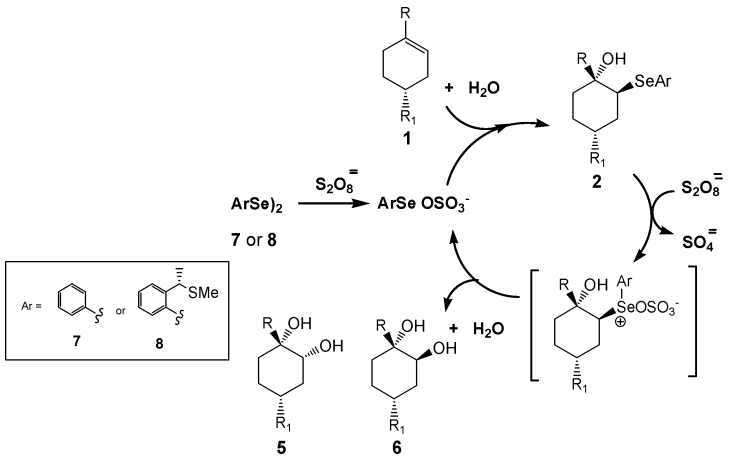


SCHEME 2

Based on these preliminary results, we investigated the first example of a multi-step one-pot selenium mediated synthesis of 1,2-diols. The reaction is promoted by the $ArSeOSO_3H$ generated in situ by oxidation of diselenide **7** or **8** with $(NH_4)_2S_2O_8$ at reflux in a 3:1 mixture of MeCN-H_2O and presumably proceeds according to the mechanism reported on Scheme 3.

The results summarized in Table II clearly indicate that the reaction leads to the formation of a couple of diols (**5,6**) in a ratio that depends on the nature of the substrate. A stoichiometric amount of the catalyst (**7**) affects the yields and the diastereoselectivity positively, and in all the cases, at the end of the reaction, it can be completely recovered.

By replacing diphenyl diselenide with the chiral di-6-[(1*S*)-1-methylthio]ethyl]phenyl] diselenide (**8**) the 1-phenylcyclohexene can be stereospecifically converted into the corresponding *cis*-1,2-diol with good yield and excellent facial selectivity (Table II, entry 8).



SCHEME 3

CONCLUSIONS

To the best of our knowledge, this is the first example in which the phenylseleno group is directly substituted by a hydroxy function. The reaction can be realized in "one pot" using the diselenide as catalyst in the presence of an excess of ammonium persulfate affording the formation of enantiomerically enriched diols. Further applications of this reaction are actually under investigation.

EXPERIMENTAL[6]

All the starting materials were commercial products and were used without further purification. In a typical procedure to a solution of diselenide (0.05 mmol or 0.5 mmol) and ammonium persulfate (3 mmol) in

TABLE II One-Pot Selenium Mediated Synthesis of 1,2-Diols

Entry	R	R_1	Diselenide (%)	**5/6**	Yield (%)	Ee (%)
1	Me	i-Pr	**7** (10)	35:65	60	100 (**5**) 100 (**6**)
2	Me	i-Pr	**7** (100)	30:70	90	100 (**5**) 100 (**6**)
3	Me	H	**7** (10)	72:28	35	—
4	Me	H	**7** (100)	80:20	90	—
5	Ph	H	**7** (10)	65:35	37	—
6	Ph	H	**7** (100)	95:5	85	—
7	Ph	H	**8** (10)	100:0	40	20(**5**)
8	Ph	H	**8** (100)	100:0	80	99 (**5**)

MeCN (3 mL) and water (1 mL) 1 mmol of olefin **1** was added. The reaction was stirred at reflux for 12–24 h. The crude product was purified by flash chromatography on a silica gel column using a mixture of diethyl ether-dichloromethane (99:1) as eluant. All the compounds were fully characterized by ^{1}H-NMR, ^{13}C-NMR experiments and by GC-MS analysis. Selected physical and spectral data are reported below.

(1*S*, 2*S*)-1-Phenyl-1,2-dihydroxycyclohexane[7]

$C_{12}H_{16}O_2$, Oil $[\alpha]_D^{20.8} = -12.8$ (c=0.52, $CHCl_3$) IR (HATAR): ν(2OH) = 3504.99 cm^{-1}; ^{1}H NMR δ 7.55–7.50 ppm (m, 2H, 2C*H*Ar), 7.40–7.35 (m, 2H, 2C*H*Ar), 7.30–7.25 (m, 1*H*, CHAr), 3.99 (dd, 1*H*, ^{3}J=4.5 Hz, ^{3}J = 11.0 Hz, C*H*OH), 2.70–2.60 (br, s, O*H*), 1.90–1.80 (m, 3H), 1.80–1.60 (m, 4H), 1.60–1.50 (m, 1H), 1.45–1.40 (m, 1H); ^{13}C NMR δ 146.3, 128.4, 126.9, 125.1, 75.7, 74.5, 38.5 29.2, 24.3, 21.0; GC-MS (70 eV): m/z (%): 192 (73) [$M^{+\cdot}$], 174 (31), 145 (16), 133 (100), 120 (50), 105 (66), 91 (22), 77 (39), 70 (13), 55 (24).

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[6] ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.62 MHz, respectively, on a Bruker Avance-DRX 400 instrument. Unless otherwise specified, $CDCl_3$ was used as the solvent and TMS as internal standard. GC-MS analyses were carried out with an HP-6890 gas chromatograph (dimethyl silicone column, 12.5 m) equipped with an HP-5973 mass-selective detector. IR spectra were recorded on a JASCO FT/IR-410 spectrophotometer using a multiple reflection horizontal ATR (HATR) accessory. Optical rotations were measured with a JASCO DIP-1000 digital polarimeter.

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